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10/623,930	07/21/2003	Vicki Bowman Vance	9536-3	6465
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MYERS BIGEL SIBLEY & SAJOVEC			EXAMINER	
PO BOX 37428			KUMAR, VINOD	
RALEIGH, NC 27627			ART UNIT	PAPER NUMBER
			1638	
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			11/14/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/623,930

Applicant(s)

VANCE ET AL.

Examiner

Vinod Kumar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-19, 21, 22, 24 and 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 20, 23 and 26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |  |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)                        |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>08/20/07</u> . | 6) <input type="checkbox"/> Other: _____   |

## **DETAILED ACTION**

### ***Status of objections and rejections***

1. Office acknowledges the receipt of Applicant's response filed in the paper of August 20, 2007. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-26 are pending. Claims 20, 23 and 26 are examined on merits in this Office action.

### ***Election/Restriction***

2. Claims 1-19, 21-22, and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 31, 2006. The restriction was made FINAL in the Office action mailed on May 16, 2006.

This application contains claims 1-19, 21-22, and 24-25 drawn to inventions nonelected with traverse in the reply filed on March 31, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

***Claim Rejections - 35 USC § 112***

3. Claims 20, 23, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for their recitation "an miRNA sequence incorporated into the plant miRNA precursor" in lines 5-6, which is confusing since it can be interpreted that "the plant miRNA precursor" has an additional miRNA sequence besides its own endogenous miRNA sequence, or it can be interpreted that the endogenous miRNA sequence of said miRNA precursor is replaced by an miRNA sequence. It is also unclear whether the recitation "an miRNA sequence" refers to endogenous or exogenous miRNA sequence. It is unclear what is intended?

Claims 20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for their recitations "plant miRNA precursor is modified" in line 10, which is confusing since it is unclear whether the recitation is referring to modifications anywhere in the "plant miRNA precursor" or only in the endogenous miRNA sequence in said miRNA precursor. It is unclear what is intended.

Claim 26 is also rejected because it fails to overcome the deficiency of claims 20.

Appropriate corrections/clarifications are required.

4. Claims 20, 23 and 26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plant cell or plant transformed with

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an miRNA precursor construct comprising a promoter operably linked with a nucleotide sequence encoding a plant miRNA precursor sequence which is modified to contain a non-native miRNA sequence replacing the native or endogenous miRNA sequence in said miRNA precursor sequence, and wherein said non-native miRNA sequence is complementary to a portion of a target sequence of interest expressed from the plant genome, does not reasonably provide enablement for a plant cell or plant transformed with an miRNA precursor construct comprising a nucleotide sequence encoding a plant miRNA precursor sequence which is modified by an incorporating an miRNA sequence into said plant miRNA precursor sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record stated in Office actions mailed on March 20, 2007.

Claims 20 and 23 are directed to a plant miRNA precursor comprising incorporating a miRNA sequence in the plant miRNA precursor sequence. The specification provides guidance on making an artificial miRNA precursor by replacing the endogenous miRNA sequence in a miRNA precursor with a miRNA sequence(s) which is complementary to a target sequence of interest. As discussed above, however, the current claim language can encompass the embodiment wherein an additional miRNA sequence is "incorporated into" the miRNA precursor, rather than replacing the native "miRNA sequence" with another. Neither the state of art at the time claimed invention was made nor the specification provides guidance on designing an artificial miRNA precursor by incorporating an additional miRNA sequence in a naturally

occurring plant miRNA precursor sequence without affecting secondary structure and stable free energy of the modified precursor molecule. This is especially important, as Applicants have argued in previous responses that secondary structure needs to be preserved. Also see page 13, 4<sup>th</sup> paragraph, wherein Applicant admits that the present invention alters only the miRNA and the strand opposite the miRNA. This implies that the instantly claimed invention is directed only to replacing endogenous miRNA with an exogenous miRNA in a plant miRNA precursor.

In the absence of any guidance, undue experimentation would have been required by a skilled artisan to determine how to modify a plant miRNA precursor by incorporating an additional miRNA sequence(s) to a naturally occurring plant miRNA precursor sequence, so that the artificial miRNA precursor molecule comprising more than one miRNA sequences (native and non-native) is capable of undergoing normal biogenesis upon its expression in a plant. Applicant's attention is drawn to the paragraph bridging pages 8-9 of Office action mailed on March 20, 2007, wherein enablement issue with regard to designing an artificial miRNA precursor comprising more than one miRNA sequence in said artificial miRNA precursor is discussed. Applicant's traversal filed in the paper of August 20, 2007 has failed to address this issue.

In the absence of adequate guidance at the time of filing, it is maintained that undue experimentation would have been required by a skilled artisan to determine how to design (make) a plant miRNA precursor comprising incorporating a miRNA sequence which is complementary to a target sequence of interest, so that when expressed in a

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transgenic plant said modified plant miRNA precursor undergoes normal biogenesis to produce desired gene silencing effect in said transgenic plant. See Genentech, Inc. v. Novo Nordisk, A/S, USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Claim 26 is also rejected because it fails to overcome the deficiencies of claim 20.

Accordingly, the rejection is maintained.

5. Claims 20, 23 and 26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention at the time of filing for the reasons of record stated in Office actions mailed on March 20, 2007.

It is maintained that claims 20 and 23 are directed to a modified plant miRNA precursor, comprising a non-native miRNA sequence and a modified miRNA sequence incorporated into said plant miRNA precursor. The specification does not have adequate written description for the genus of plant miRNA precursor sequences comprising a native and non-native miRNA sequences under current written description guidelines. It is maintained that Applicants have failed to describe undisclosed structures of their broadly claimed genus, and one skilled in the art cannot reliably predict these structures based on the disclosure of modified miRNA 167 and miRNA 171 precursor comprising

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an exogenous miRNA sequence which replaces their native or endogenous miRNA sequence. The claims encompass structures of a broadly claimed genus whose function has not been correlated with regulating the expression of a target sequence of interest when expressed in a plant cell or plant. Applicants have failed to describe common functional domains or elements shared by the undisclosed structures of their broadly claimed genus. Thus, it is evident that Applicant's broadly claimed genus was not reduced to practice. Accordingly, there is lack of adequate description to inform a skilled artisan that applicant was in possession of the claimed invention at the time of filing.

Also see in re Curtis (69 USPQ2d 1274 (Fed. Cir.2004), where the court held that there was sufficient evidence to indicate that one of ordinary skill in the art could not predict the operability of other species other than the single one disclosed in the specification. The court held that a disclosure naming a single species can support a claim to a genus that includes that species if a person of ordinary skill in the art, reading the initial disclosure, would "instantly recall" additional species of the genus already "stored" in the minds, but if other members of the genus would not "naturally occur" to a person of ordinary skill upon reading the disclosure, then unpredictability in performance of species other than specifically enumerated defeats claims to the genus.

Applicant's response filed in the paper of August 20, 2007 is directed to the genus of modified plant miRNA precursors comprising replacing endogenous miRNA sequence with a non-native miRNA sequence. The response fails to address the genus



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of modified plant miRNA precursors containing a native and a non-native miRNA sequence in said modified miRNA precursor sequences.

For at least these reasons and the reasons of record stated in the previous Office Action, the requirement for written description has not been met.

6. Claims 20, 23, and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) Neither the instant specification nor the originally filed claims appear to provide support for the phrase "plant miRNA precursor is modified to correspond to the modifications made in the miRNA, the modifications to the plant miRNA precursor" in part (b) in claims 20 and 23. The instant specification, provides support for a modification of a plant miRNA precursor by replacing its endogenous miRNA sequence with an exogenous miRNA sequence which is complementary to a target mRNA sequence. However, the breadth of the phrase "plant miRNA precursor is modified to correspond to the modifications made in the miRNA, the modifications to the plant miRNA precursor" encompasses modifications anywhere within the miRNA precursor sequence and not just within the miRNA sequence. The specification fails to provide support for the full scope of the instantly claimed phrase, "plant miRNA precursor is modified to correspond to the modifications made in the miRNA, the modifications to the

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plant miRNA precursor". Thus, such phrase constitutes NEW MATTER. In response to this rejection, Applicant is required to point to support for the phrases "plant miRNA precursor is modified to correspond to the modifications made in the miRNA, the modifications to the plant miRNA precursor" or to cancel the new matter.

(B) Neither the instant specification nor the originally filed claims appear to provide support for the phrase "an miRNA sequence incorporated into the plant miRNA precursor, wherein the miRNA is modified as compared with the miRNA sequence endogenous to said isolated plant miRNA precursor" in claims 20 and 23. The instant specification provides support for replacing the endogenous miRNA sequence of an miRNA precursor with an exogenous miRNA sequence. However, the breadth of the phrase "an miRNA sequence incorporated into the plant miRNA precursor, wherein the miRNA is modified as compared with the miRNA sequence endogenous to said isolated plant miRNA precursor" encompass modifications within the miRNA precursor without replacing the endogenous miRNA sequence with an exogenous miRNA sequence. The specification fails to provide support for the full scope of instantly claimed phrases "an miRNA sequence incorporated into the plant miRNA precursor, wherein the miRNA is modified as compared with the miRNA sequence endogenous to said isolated plant miRNA precursor". Thus, such phrase constitutes NEW MATTER. In response to this rejection, Applicant is required to point to support for the phrase "an miRNA sequence incorporated into the plant miRNA precursor, wherein the miRNA is modified as compared with the miRNA sequence endogenous to said isolated plant miRNA precursor" or to cancel the new matter.

***Claim Rejections - 35 USC § 103***

7. Claims 20, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cullen et al. (US Patent Publication No. 2004/0053411, Published March 18, 2004, Filed May 5, 2003, Provisional application filed May 3, 2002) in view of Llave et al. (The Plant Cell, 14:1605-1619, Published July 1, 2002, Applicant's IDS) and Reinhart et al. (Genes and Development, 16:1616-1626, Published July 1, 2002).

Claims are drawn to a plant cell, plant or transformed seed of said plant comprising stably transformed with an miRNA precursor construct, said precursor, said miRNA precursor construct comprising a promoter functional in a plant, wherein the promoter is operably linked to a nucleotide sequence encoding an isolated plant miRNA precursor, said plant miRNA precursor having an miRNA sequence incorporated into the plant miRNA precursor, wherein (a) the miRNA is modified as compared with the miRNA sequence endogenous to said isolated plant miRNA precursor, the modifications maintaining the length of the endogenous miRNA; and (b) the isolated plant miRNA precursor is modified to correspond to the modifications made in the miRNA, the modifications to the plant miRNA precursor maintaining the secondary structure of the plant miRNA precursor including double strandedness and any mismatches, and further wherein, the modified miRNA is complementary to and hybridizes with a target nucleotide sequence within said plant whereby the expression of the target sequence is reduced.

Cullen et al. teach designing an artificial miRNA precursor by modifying a naturally occurring miRNA precursor sequence with an exogenous miRNA to target and post-transcriptionally silence a gene of interest in a cell. The reference teaches that said modification comprises incorporating an miRNA sequence of interest into said miRNA precursor by substituting stem sequences of its native miRNA to generate miRNAs suitable for use in inhibiting expression of any target gene of interest in any host cell including a plant cell. The reference clearly teaches that bulges may be present in the sequence. The reference further teaches expressing said artificially designed miRNA precursor from a DNA expression vector in any host cell, including a plant cell. The reference also teaches that the modified or artificial miRNA precursor undergoes normal biogenesis to release non-native miRNA which participates in post-transcriptional gene silencing of the target gene of interest. See in particular, paragraphs 0009; Figures 1-8; paragraphs 0022, 0024-0027, 0029, 051-0053, 0057-0058.

Cullen et al. do not teach a plant miRNA precursor.

Llave et al. teach a number of plant miRNA precursors comprising an endogenous miRNA sequence. The reference also teaches that plant miRNA precursors contain short and simple stem-loop structures. The reference further teaches that plant miRNAs are small (predominately 21 to 24 nucleotides in length), arise by processing of miRNA precursor transcripts (~ 70 nucleotides) containing imperfectly paired stem structures in a Dicer-dependent manner. The reference further

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teaches cloning, sequencing and predicting secondary structures of said precursors which are capable of undergoing normal biogenesis to produce miRNA. The reference further teaches that plant miRNAs comprise a sequence which is complementary to a portion of an endogenous gene sequence whose expression is regulated by said miRNA sequence through perfect or nearly perfect binding to the endogenous target sequence. The reference also teaches a method of making a transgenic plant comprising transformation of a plant with a DNA construct comprising a mRNA inhibitory sequence (dsRNAi) operably linked to promoter functional in plant. See in particular, page 1605, abstract; page 1608, table 1; page 1609, figure 4; page 1611, table 2; page 1612, table 3; page 1613, figure 6; page 1614, figure 7; page 1617, sequence accession numbers.

Reinhart et al. teach plant miRNA precursors comprising an endogenous miRNA sequence which is released during the processing of the miRNA precursor to play a role in post-transcriptional gene regulation of specific endogenous plant gene(s). The reference further teaches cloning, sequencing and predicting fold-back secondary structures (using RNAfold program) of said precursors which are capable of undergoing normal biogenesis to produce miRNA. Reinhart et al. also teach that said plant miRNA precursor comprises few mismatches in the miRNA sequence resulting in bulges. See in particular, abstract; page 1618, table 1; page 1619, figure 1; page 1622, figure 4.

At the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to use the method of silencing the expression of a desired gene in a cell as taught by Cullen et al., to silence a desired gene in a plant or plant cell.

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It would have been obvious to use a recombinant DNA encoding a plant miRNA precursor sequence as taught by Llave et al. or Reinhart et al. and modify the plant miRNA precursor sequence by replacing the native miRNA sequence with an exogenous miRNA sequence which is complementary to a gene transcript of interest for down-regulating or silencing the expression of said desired gene in a plant cell or plant. One would have used any plant transformation vector and method to make the plant cell or plant, including the one taught by Llave et al.

Given that Llave et al. and Reinhart et al. teach that a plant miRNA precursors comprising a native miRNA sequence which regulates the expression of specific plant gene, and Cullen et al. teach designing artificial (same as modified) miRNA precursor comprising incorporating an exogenous (non-native) miRNA sequence of interest into a naturally occurring miRNA precursor, one of ordinary skill in the art would have been motivated to modify a naturally occurring plant miRNA precursor by incorporating an exogenous miRNA sequence which is complementary to a target transcript of interest within the plant. One of ordinary skill in the art would have been motivated to do so for the purpose of down-regulating the expression of any target gene of interest, depending on ones desired end.

Given that many native miRNA sequences contain mismatches or "bulges" as seen in Llave et al. and Reinhart et al., it would have been obvious to maintain the size, and positions of mismatches of the native miRNA secondary structure in the non-native

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miRNA sequence of the modified plant miRNA precursor, to avoid any possible problems during processing of the miRNA precursor.

Given that Cullen et al. teach that transcribing a miRNA precursor from a vector in a plant cell host, opens up the possibility of long term stable gene-silencing of a target gene of interest, one of ordinary skill in the art would have been motivated to express said modified plant miRNA precursor sequence in a transgenic plant for the purpose of studying the function of a target gene of interest in growth and development for example, with reasonable expectation of success. Obviously seeds would have also been produced for the purpose of propagation of said transgenic plants.

Thus, the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

### ***Conclusions***

8. Claims 20, 23, and 26 remain rejected.

### ***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vinod Kumar whose telephone number is (571) 272-4445. The examiner can normally be reached on 8.30 a.m. to 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

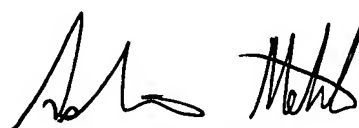
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A handwritten signature in black ink, appearing to read 'Ashwin D. Mehta', is positioned above the printed name.

**ASHWIN D. MEHTA, PH.D.**  
**PRIMARY EXAMINER**